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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,793	JOHANSEN ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-83 and 87-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-83 and 87-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/27/08 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 3/27/08 is acknowledged. Claims 1-79 and 84-86 are cancelled. Claim 80 is amended. Claims 91-93 are newly added. Claims 80-83, 87-90 and newly added claims 91-93 are pending in this application and under examination in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

5. Applicant's arguments filed on 3/27/08 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Specification

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The instant invention is directed to a method of treatment not a product, neurotrophic factor.

Claim Rejections/Objections Maintained

In view of the amendment filed on 3/27/08, the following rejections are maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 80-83, 87-90 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,749 (Yan et al.,issued June 24, 1997) in view of US 6,284,540 (Milbrandt et al., issued Sep 4, 2001, filed December 24, 1998; as in IDS).

The rejection is maintained for the reasons made of record in the previous office action, and as follows.

At p. 5-7 of the response, Applicant argues that neublastin/artemin is structurally and functionally distinct from GDNF because neublastin/artemin only shares 34-36% identity to GDNF and binds to GFRα3 with high affinity, and GDNF only binds to GFRα1 but does not bind to GFRα3. Applicant arguments have been fully considered but they are not persuasive.

In contrast, although Neublastin/artemin binds to GFRα3, Milbrandt (US 6,284,540) teaches that Neublastin/artemin can also bind and activate GFRα1. Yan (US 5,641,749) teaches a method of treating retinal ganglion cell degeneration caused by glaucoma by the intraocular implantation of glial cell line-derived neurotrophic factor (GDNF)-expressing cells (see paragraph spanning columns 4-5, and column 19, lines 28-30) and Milbrandt teaches that Neublastin/artemin is a member of the GDNF family and can bind and activate GFRα1 (i.e. the receptor for GDNF). Thus, it would have been obvious to substitute GDNF in the method of Yan (US 5,641,749) with Neublastin/artemin or cells expressing Neublastin/artemin as disclosed by Milbrandt in treatment of glaucoma or retinal degenertion because Neublastin/artemin is a member of the GDNF family, which would be expected to act similarly to GDNF, and has been shown to activate GFRa1. Note that

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.,* 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

At p. 6 of the response, Applicant argues that there is no motivation or suggestion to combine the applied references to achieve the claimed method because Milbrandt does not teach a method of treating Neublastin/artemin in treatment of macular degeneration, glaucoma or retinitis pigmentosa and Yan only teaches use of GDNF in treatment of retinal ganglion cell degeneration. Applicant arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. *Pro Mold Tool Col. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP. §2144.07.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involve not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See *CTS Corp. v. Electro Materials Corp. of America* 202 USPQ 22 (DC SNY 1979); and *In re Burckel* 201 USPQ 67 (CCPA 1979).

In this case, Yan et al. disclose methods of treating retinal ganglion cell degeneration caused by glaucoma by the intraocular implantation of glial cell line-derived neurotrophic factor (GDNF)-expressing cells (see paragraph spanning columns 4-5, and column 19, lines 28-30). Although Yan does not teach use of Neublastin/artemin,

Milbrandt teaches that artemin (i.e., Neublastin) is a member of the GDNF neurotrophic factor family and is useful for treating conditions involving neuronal degeneration. Further, Milbrandt teaches that Neublastin/artemin can bind and activate both GFRα1 and GFRα3. Since Neublastin/artemin is a member of the GDNF family and can bind and activate GFRα1 (i.e. the receptor for GDNF), it would have been expected that neublastin/artemin would act and function as GDNF and are effective in treatment of retinal degeneration as disclosed by Yan. Thus, a skilled artisan would have been motivated with an expectation of success in substituting GDNF in the Yan's method with neublastin/artemin since neublastin/artemin also bind and activate GFRα1, a receptor for GDNF. Accordingly, the combined teachings of the above references render obvious the instant method of claims 80-83, 87-90 and 93.

8. Claims 80-83 and 87-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,749 (Yan et al.,issued June 24, 1997) in view of US 6,284,540 (Milbrandt et al., issued Sep 4, 2001, filed December 24, 1998; as in IDS) as applied to claims 80-83, 87-90 and 93 above, and further in view of US 6299895 (Hammang et al. issued Oct 9, 2001, filed Mar 24, 1997, published Sep 25,1997).

US 5,641,749 (Yan) and US 6,284,540 (Milbrandt) are as set forth above but do not teach treatment of macular degeneration and retinitis pigmentosa as recited in instant claims 80, 91 and 92.

US 6299895 (the '895 patent) teaches use of GDNF in treatment of macular degeneration and retinitis pigmentosa as recited in instant claims 80, 91 and 92 (see

col.5, lines38-64; col. 10, line 16-col.11, line 67; examples 1-5). The '895 patent teaches a method and a device to deliver biological active molecule including cells, growth factors such as GDNF or other neurotrophic factors or other agents to eyes to treat different eye disorders including macular degeneration and retinitis pigmentosa as recited in instant claims 80, 91 and 92 (see col.5, lines38-64; col. 10, line 16-col.11, line 67; examples 1-5).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the teachings of US 5,641,749 (Yan) and US 6,284,540 (Milbrandt) with the teaching of US 6299895 to treat macular degeneration and retinitis pigmentosa with Neublastin/artemin. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because Yan and the '895 patent teaches treatment of different eye disorders including macular degeneration and retinitis pigmentosa and glaucoma with GDNF and Milbrandt teaches that Neublastin/artemin can function as GDNF to bind and activate GFRα1. So it would have been obvious to substitute GDNF in the methods of Yan and the '895 patent in treatment of different eye disorders with Neublastin/artemin because Neublastin/artemin is predicted to be function as GDNF as taught by Milbrandt.

New Grounds of Rejection Necessitated by the Amendment

The following rejections are new grounds of rejections necessitated by the amendment filed on 3/27/08.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-83 and 87-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating photoreceptor loss in the retina of patients afflicted with macular degeneration, retinitis pigmentosa, or glaucoma, comprising administering to the eye of said patient a cell line expressing a Neublastin polypeptide comprises one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 9-12, does not reasonably provide enablement for a method of treating the above eye disorders comprising administering a cell line expressing a Neublastin polpeptide, which comprises an amino acid sequence that is at least 9 95% homologous to the amino acid sequence of SEQ ID NO: 12 or comprising any amino acid sequences of SEQ ID NOs 9-12 (i.e. including undefined fragments) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is reinstated and maintained for the reasons below.

Based on the specification (p. 2 of the instant specification), the recited Neublastin polypeptide encompasses fragments, variants and derivatives of wild type Neublastin, SEQ ID NO:2.

> A "neublastin polypeptide," as used herein, is a polypeptide which possesses neurotrophic activity (e.g., as described in Examples 6, 7, 8, and 9) and includes those polypeptides which have an amino acid sequence that has at least 70% homology to the human "neublastin" polypeptides …, and variants and

derivatives thereof. In addition, this invention contemplates those polypeptides which have an amino acid sequence that has at least 70% homology to the murine "neublastin" polypeptides set forth in AA,-AA224 of SEQ. ID. NO. 16."

However, the specification fails to provide sufficient guidance as to how to make and use these structurally undefined variants and derivatives. The specification fails to provide sufficient guidance as to what other structures/amino acid sequences could/could not be included/changed in all Neublastin polypeptides including fragments, variants and derivatives in order to preserve the activity of wild type Neublastin SEQ ID NO:2 in treating an eye disorder such as macular degeneration, retinitis pigmentosa or glaucoma. Applicant fails to provide sufficient guidance as to whether all Neublastin polypeptides including fragments, variants and derivatives could be used in the claimed method since a single amino acid change could abolish the binding ability of a molecule. For example, a substitution of lysine residue by glutamic acid at position 118 of acidic fibroblast growth factor results in a substantial loss of its biological activity including the binding ability to heparin and its receptor (Burgess et al. J of Cell Bio. 111:2129-2138, 1990).Thus, it is unpredictable whether other Neublastin polypeptides can be used in the claimed method, indicating that undue experimentation is required to practice the claimed invention.

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the

changes which can be made and still maintain activity is unpredictable and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

Therefore, in view of the breadth of the claims, the lack of guidance in the specification, the unpredictability of the invention, and the current status of the prior art, undue experimentation would be required by a skilled artisan to perform in order to practice the claimed invention as it pertains to a method for treating an eye disorder including macular degeneration, retinitis pigmentosa or glaucoma comprising administration of a cell line expressing a Neublastin polypeptide..

10. Claims 80-83 and 87-93 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 80-83 and 87-93 are drawn to a method for treating an eye disorder including macular degeneration, retinitis pigmentosa or glaucoma comprising administration of a cell line expressing a Neublastin polypeptide. The claims encompass use of a genus of Neublastin polypeptide. Applicant has not disclosed sufficient species for the broad genus of Neublastin polypeptides. The specification only describes Neublastin polypeptides comprising the amino acid sequences selected from SEQ ID NOs 9-12 to be used in the claimed method. However, the claims are not limited to the SEQ ID NO:s 9-12 as set forth above but also includes variants and derivatives because the specification defines a Neublastin polypeptide encompassing variants and derivatives.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant is in possession of and what Applicant is claiming. From the specification, it is clear that Applicant is in possession of SEQ ID NOs:9-12 that can be predictably used in the claimed method. Although the specification describes variants and derivatives with at least 70% homology to SEQ ID NO: 12 on p. 2 of the specification, Applicant is not in possession of these variants and derivatives as described in the specification in treating the claimed eye disorders. There is no identification of any particular portion of the structure that must be conserved. The instant specification fails to provide sufficient descriptive information, such as definitive

structural or functional features of the claimed genus of Neublastin polypeptides. There is no description of the conserved regions which are critical to the function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure of variants and derivatives to SEQ ID NO:2 function. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify other Neublastin variant polypeptides might be. Since the common characteristics/features of other Neublastin variant polypeptides are unknown, a skilled artisan cannot envision the functional correlations of the genus with the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of proteins.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement

that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, a method for treating an eye disorder by administration of a Neublastin polypeptide has not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement. See MPEP § 2163.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 80-83 and 87-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 80-83 and 87-93 are indefinite because independent claim 80 recites “greater specificity”. The rest of claims are indefinite as depending from an indefinite claim 80. The term "greater specificity” in claim 80 is a relative term which renders the claim indefinite. The term "greater" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant fails to set forth the metes and bounds of what is encompassed within the definition of “greater specificity”. Since the metes and bounds are not unknown, a skilled artisan can not determine to what degree of the binding would be considered as greater specificity as recited in the claim. Thus the claims are indefinite.

Conclusion

12. NO CLAIM IS ALLOWED.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

US Patent No. 6361771 (Tao et al., issued Mar 26, 2002, priority Apr 6, 1999) teaches use of GDNF in treatment of macular degeneration, retinitis pigmentosa.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
May 28, 2008

/Christine J Saoud/
Primary Examiner, Art Unit 1647